Network-based predictions of *in vivo* cardiac hypertrophy

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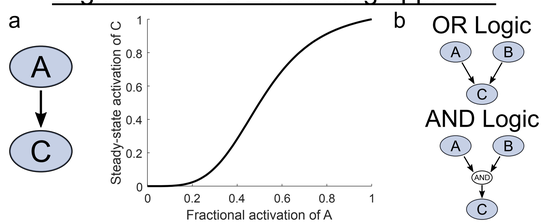
Introduction

- Cardiac hypertrophy is a common response of cardiac myocytes to stress and a predictor of heart failure. While *in vitro* cell culture studies have identified numerous molecular mechanisms driving hypertrophy, it is unclear to what extent these mechanisms can be integrated into a consistent framework predictive of *in vivo* phenotypes.
- We investigate the degree to which an *in vitro*-based manually curated computational model[1] of the cardiac hypertrophy signaling network is able to predict *in vivo* hypertrophy of 52 cardiac-specific transgenic mice.
- The model provides a framework with which to mechanistically integrate data from multiple laboratories and experimental systems to predict molecular regulation of cardiac hypertrophy.

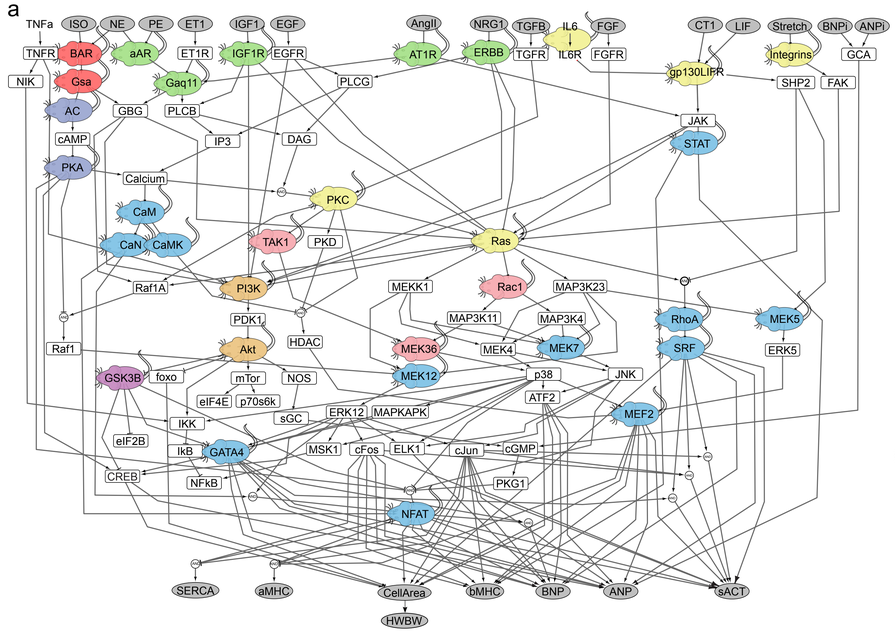
Logic-based ODE modeling approach



$$\frac{dC}{dt} = \frac{1}{\tau_C}(W_{AC} f_{act}(A) C_{max} - C) \qquad f_{act}(X) = \frac{VX^n}{K^n + X^n}$$

Figure 1. The cardiac hypertrophy signaling network uses a logic-based ODE modeling approach[2]. (a) Simple 2 node reaction in which node A activates node C. Differential equation for node C and normalized Hill equation for generalized node X are shown. (b) Schematic representation of OR logic gates (either A or B can activate C), and AND logic gates (both A and B are necessary to activate C).

Computational network model predictions and validation of transgenic overexpressing mouse models for cardiac hypertrophy



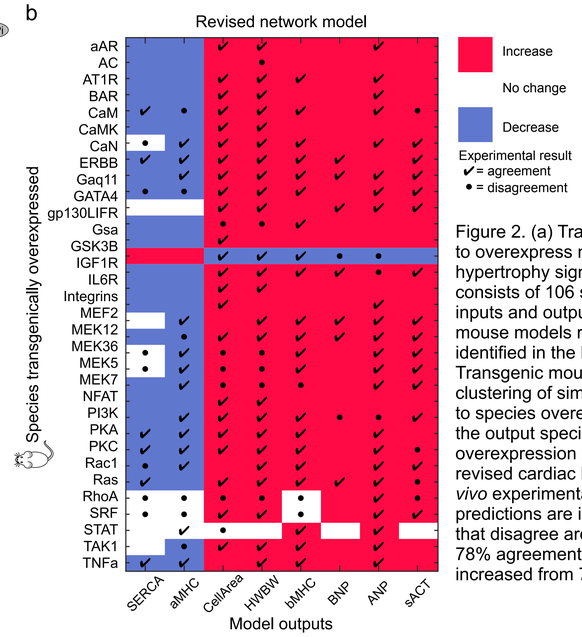


Figure 2. (a) Transgenic mouse models developed to overexpress many of the species in the cardiac hypertrophy signaling network model. The model consists of 106 species and 192 reactions. Model inputs and outputs are shown in gray. 52 transgenic mouse models representing 34 of the species were identified in the literature for this analysis. Transgenic mouse models are color-coded by clustering of similar mathematical model responses to species overexpression. (b) Model predictions for the output species (x-axis) with individual species overexpression (y-axis) are color coded for the revised cardiac hypertrophy signaling network. *In vivo* experimental data in agreement with the model predictions are indicated by a check (✔) and data that disagree are indicated by a dot (●). There is 78% agreement in the revised model, which is increased from 72% in the original model.

Intermediate species validation and modular relationships of network species and mice

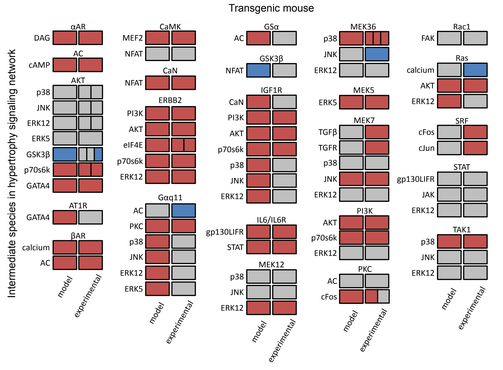


Figure 4 (right). Network activation by modular relationships of species and mice. K-means clustering allowed condensation of the 107 network model species into 8 functional modules (y-axis) and clustering of the 34 species for which transgenic (TG) overexpressing mice exist into 8 groups (x-axis) with the most similar network responses. The predicted average response of each module is shown for overexpression of an individual species.

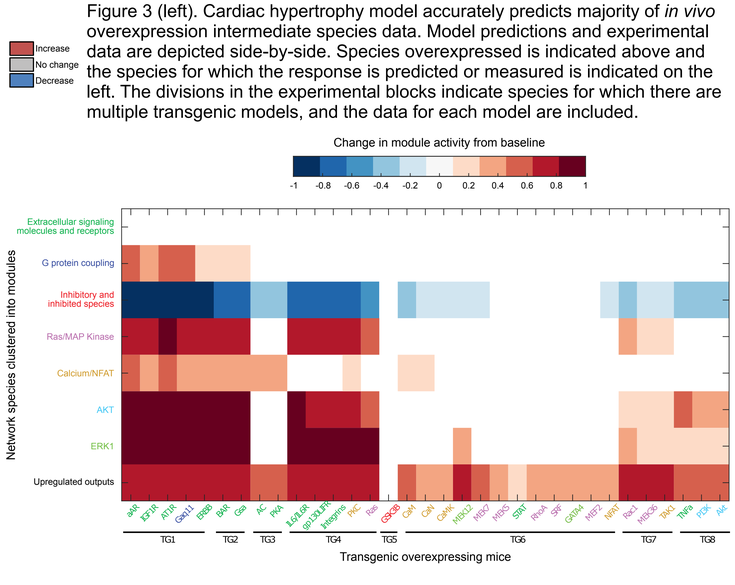


Figure 3 (left). Cardiac hypertrophy model accurately predicts majority of *in vivo* overexpression intermediate species data. Model predictions and experimental data are depicted side-by-side. Species overexpressed is indicated above and the species for which the response is predicted or measured is indicated on the left. The divisions in the experimental blocks indicate species for which there are multiple transgenic models, and the data for each model are included.

Double transgenic predictions using *in vivo* hypertrophy signaling network

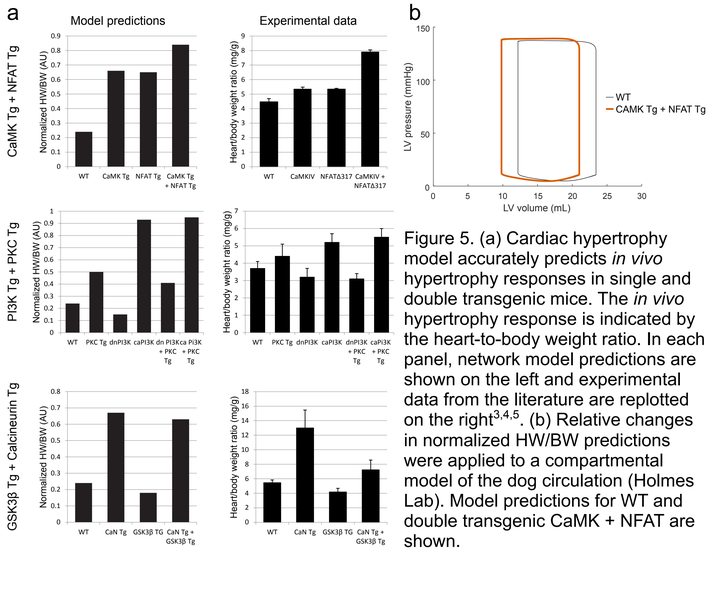


Figure 5. (a) Cardiac hypertrophy model accurately predicts *in vivo* hypertrophy responses in single and double transgenic mice. The *in vivo* hypertrophy response is indicated by the heart-to-body weight ratio. In each panel, network model predictions are shown on the left and experimental data from the literature are replotted on the right[3,4,5]. (b) Relative changes in normalized HW/BW predictions were applied to a compartmental model of the dog circulation (Holmes Lab). Model predictions for WT and double transgenic CaMK + NFAT are shown.

Conclusions

- We show that an *in vitro*-based computational model of cardiac hypertrophy is able to predict *in vivo* hypertrophy with minor revisions.
- Analysis of double transgenic mouse models reveals that the computational model is able to robustly predict tissue-level responses in mice subjected to multiple, simultaneous perturbations.

Acknowledgements

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